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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,769	10/25/2000	Darwin J Prockop	57616-5018US1	4022

23973 7590 08/08/2006

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,769	PROCKOP ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-29 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 18, 2006 has been entered.

Claims 13, 30, 37-41 are cancelled. Claim 24 is amended. Applicant indicates that claim 24 has been amended to correct a typographical error (Applicant's response, page 8). This is acknowledged.

Claims 1-12, 14-29, 31-36 are under consideration.

Withdrawn Rejections

35 U.S.C. § 102 (b)

Applicant's arguments, see pages 8-11 of Applicant's response, filed May 18, 2006, with respect to the rejection of claims 1-12, 14-29, 31-36 have been fully considered. As indicated in the Advisory Action of May 18, 2006, which seems to have crossed in the mail with Applicant's Request for Continued Examination, the 102 rejection as it applies to the claims is withdrawn. The rejection of claims 1-12, 14-29, 31-36 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 22-29 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of inducing proliferation of isolated human marrow stromal cells in vitro by plating and replating cells, wherein said cells are plated at an initial density of less than about 50 cells per square centimeter of growth surface, the method comprising

1) providing the isolated human marrow stromal cells and a growth medium comprising mammalian serum or growth medium supplemented with conditioned medium, wherein the conditioned medium is obtained from a culture of producer human marrow stromal cells plated at an initial density of at least about 0.5 cells per square centimeter and which are incubated for at least about 3 days to a growth surface such that the initial density of the isolated human marrow stromal cells is less than about 50 cells per square centimeter of growth surface,

2) incubating the plated cells of step (1) under growth-promoting conditions, whereby the human marrow stromal cells proliferate, and

3) replating the proliferated marrow stromal cells with growth medium comprising mammalian serum or growth medium supplemented with conditioned medium, wherein the conditioned medium is obtained from a culture of producer human marrow stromal

cells plated at an initial density of at least about 0.5 cells per square centimeter and which are incubated for at least about 3 days to a second growth surface at least one time such that the initial density of the replated isolated human marrow stromal cells is less than about 50 cells per square centimeter of growth surface, wherein the replating allows the cells to expand by a factor of at least 10-fold,

does not reasonably provide enablement for

a method of inducing proliferation of isolated human marrow stromal cells in vitro by plating and replating cells, wherein said cells are plated at an initial density of less than about 50 cell per square centimeter of growth surface, the method comprising

1) providing the isolated human marrow stromal cells and any growth medium to a growth surface such that the initial density of the isolated human marrow stromal cells is less than about 50 cells per square centimeter of growth surface,

2) incubating the growth surface of step (1) under growth-promoting conditions, whereby the human marrow stromal cells proliferate, and

3) replating the proliferated marrow stromal cells and any growth medium to a growth surface at least one time such that the initial density of the replated isolated human marrow stromal cells is less than about 50 cells per square centimeter of growth surface, wherein the replating allows the cells to expand by a factor of at least 10-fold.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention is drawn to a method of inducing proliferation of isolated human marrow stromal cells in vitro comprising steps of plating an replating said stromal cells at a density of 50 or fewer cells per square centimeter.

While the specification and art provide guidance for an artisan to arrive at the claimed invention when using fetal bovine serum as part of the culture media (e.g. specification, page 29, lines 17-21 and page 30, line 9), the specification does not provide guidance to arrive at the claimed invention using any growth factors (e.g. claim

22). At the time of filing, the art teaches that when human marrow stromal cells were cultured with serum-free medium and a variety of possible growth factor combinations, the cells did not grow (Kuznetsov et al. 1997, British Journal of Haematology, 97: 561-570, see IDS, see page 568, 1st col., 2nd parag.). As this issue applies to the instant invention, nothing in the specification provides guidance for an artisan to overcome the fact that one or a combination of growth factors are able to induce proliferation of human marrow stromal cells plated at 50 or fewer cells per centimeter square. As such, an artisan does not know how to arrive at the claimed invention.

With regard to the claims being drawn to a method of enhancing in vitro proliferation comprising a step of supplementing growth medium with a factor present in a conditioned medium, wherein the conditioned medium is obtained from a culture of producer human marrow stromal cells (e.g. claim 24), nothing in the specification or art provides guidance what "factor" is envisioned to be added to media such that an artisan could arrive at the claimed invention. This is an issue because as discussed above in the previous paragraph, the art teaches that no known growth factor or combination of growth factors is known to induce proliferation of human marrow stromal cells. The specification teaches that conditioned medium was fractionated by HPLC and that different HPLC fractions were administered to the cultured stromal cells. Fraction 10 (comprising molecules having an average molecular weight of about 30,000) was found induce the greatest amount of proliferation and fraction 17 (comprising molecules having an average molecular weight of 10,000) was found to inhibit growth of cells (specification, page 42, 4th parag.). While the specification provides this teaching, the

specification does not provide guidance as to what "factor" or "factors" are responsible for stimulating proliferation in stromal cells, such that an artisan could readily obtain the factor(s) and arrive at the claimed invention. With regard to claim 29, wherein the growth medium is supplemented with a factor(s) having a molecular weight of 10,000, nothing in the specification teaches any 10,000 molecular weight factor that an artisan could use to induce proliferation of cells. Rather, whatever factor that was in fraction 17 inhibited proliferation, that it is not readily apparent how a factor that inhibits growth can be used to arrive at the claimed invention, a method of cell proliferation. As such, because neither the specification or art provide guidance as to what this "factor" is, an artisan cannot arrive at the claimed invention.

Thus, for these reasons, the claims are rejected.

Claims 1, 22-29 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or

chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification teaches that conditioned medium was fractioned by HPLC and that fraction 10 (containing molecules having an average molecular weight of about 30,000) exhibited the greatest proliferation-stimulating activity (specification, page 42, 4th parag.), the specification provides no guidance as to what factor(s) in fraction 10 has a proliferation-stimulating effect. On a similar note, the specification teaches a factor(s) in fraction 17 that has an inhibitory effect on the growth of human marrow stromal cells. While the specification provides this teaching, nothing in the specification or the art provide any guidance as to what factor(s) in fraction 17 has any proliferative effect such that an artisan can arrive at the claimed invention, i.e. a method of cell proliferation (e.g. claims 1 and 29). The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing

date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, while the specification teaches that a factor(s) in fraction 10 promotes cell proliferation, nothing in the specification provides any guidance as to what that factor(s). The art at the time of filing teaches that there are no known growth factors that induce proliferation in human stromal cells (Kuznetsov et al., page 586, 1st col., 2nd parag.) that an artisan cannot readily arrive at the claimed invention for any growth factor. The skilled artisan cannot envision all the possible proteins which may be secreted by the cell and has a molecular weight of 30,000 or 10,000, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no "factor" meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-29, 31-36 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step 3, is unclear with regard to "a growth surface." While "a growth surface" could mean the surface of a new, clean dish, the word "a" preceding "growth surface" does not necessarily limit an artisan to use a new, clean dish. Claims 2-12, 14-23 depend on claim 1 and are included in the rejection. This same issue occurs in claim 24 (line 9), claim 31 (line 9), claim 32 (line 9). Claims 25-30, 33-36 depend on these claims and are included in this rejection.

Claim 12 recites the limitation "second growth surface" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Claims 13-19 depend on claim 12 and are included in the rejection.

Claim 12, line 3, uses the word, "surfact." It is unclear what "surfact" is. Claims 13-19 depend on claim 12 and are included in the rejection.

Claim 24, lines 7-8, recites the limitation "the proliferated isolated marrow stromal cells." There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 14-29, 31-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al., 1997, Biotechnology Letters, 19: 89-92, for reasons of record, August 10, 2004 and March 24, 2005.

Applicant's arguments filed May 18, 2006 have been fully considered but they are not persuasive.

Applicant indicates that Huang provides no suggestion or motivation, whether alone or combined with the knowledge of one of skill in the art, to induce proliferation of marrow stromal cells by plating the cells at low density and replating the cells at a second low density such that the cells are expanded by at least 10-fold. Huang initially plates at low density, but does not teach replating (Applicant's response, page 1, 3rd parag.). In response, with regard to expansion of cells 10-fold, this would mean that the one cultured cell would need to proliferate to 10 cells. It would not be unheard of to have a colony of at least 10 cells, especially if arriving at 10 or more cell expansion can be achieved by culturing the cells for a longer period of time. As such, to replate and

arrive at a 10-fold expansion, it again would not be unheard of having one colony with at least 10 cells. Applicant indicates that there is no reasonable expectation of success if three cells lines are plated at the initial densities presently claimed and two of the cell lines fail to grow at all, and then the experiment is repeated, and the same two cell lines again fail to grow again (Applicant's response, page 12, 2nd parag.). In response, the issue focuses on the third cell line, the one that did grow, and that one viable cell line is obvious over the claimed invention.

With regard to the Applicant indicating that the Huang disclosure regarding the use of conditioned media does nothing to change the fact that the Examiner has not established a prima facie case of obviousness as each of the cell lines performed differently and reacted to conditioned media differently (Applicant's response, page 12, 4th parag.). In response, Huang's teaching that some cell lines grew better in one conditioned media better than other is not reason for unpredictability in arriving at the claimed invention. The claims minimally require plating and replating of stromal cells at low density and determining a 10-fold expansion. Again, if the cells had not proliferated 10-fold, an artisan would allow the cells to grow for a longer time until the 10-fold proliferation was achieved.

As such, the rejection of claims 1-12, 14-29, 31-36 remains.

Claims 1, 22-29, 31-36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. in view of Kuznetsov et al., 1997, J. Bone and Mineral Res., 12: 1335-1347, Azizi et al., 1998, PNAS, USA, 95: 3908-3913, Greenberger, US

Patent No. 5,766,950, and Prockop, 1997, Science, 276: 71-74 for reasons of record, August 10, 2004 and March 24, 2005.

Applicant's arguments filed May 18, 2006 have been fully considered but they are not persuasive.

Applicant indicates that Huang discloses an initial plating density with the scope of the present claims, but does not teach nor suggest replating the cells or replating the cells such that the cells are expanded by a factor of 10-fold. Applicant also indicates that none of the other references remedy Huang at teaching replating (Applicant's response, page 14, 3rd parag. under "Rejection of Claims 1, 22-29 and 31-36 Pursuant to 35 U.S.C. § 103(a)"). In response, as indicated in the Office Action, August 10, 2004, page 3, 2nd parag., the steps of replating is routine in cell culture methods where cells are cultured for several rounds to either maintain them in culture or are used to prepare new cell lines or for starting new cultures from a source, such as from tissue samples, or cloning of a single cell. Further, the Office Action also indicates that culturing cells at a low density of 50 or fewer cells per centimeter squared does not recite any specific embodiment that would make it distinct from the prior art. That is, low-density plating is often practiced in the art, especially when the artisan grow cells and use them when they grow to a certain density or when the artisan is planning on harvesting confluent cells at some remote time point.

As such, the rejection of claims 1, 22-29, 31-36 remains.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

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